

CS 466

Introduction to Bioinformatics

Lecture 17

Mohammed El-Kebir

October 23, 2019



Outline

- Two-State Perfect Phylogeny
- Multi-State Perfect Phylogeny
- Large Maximum Parsimony Phylogeny Problem
- Summary

Reading:

- Lecture notes

Maximum Parsimony

Small Maximum Parsimony Phylogeny Problem:

Given $m \times n$ matrix $A = [a_{i,j}]$ and tree T with m leaves, find assignment of character states to each internal vertex of T with minimum parsimony score.

Large Maximum Parsimony Phylogeny Problem:

Given $m \times n$ matrix $A = [a_{i,j}]$, find a tree T with m leaves labeled according to A and an assignment of character states to each internal vertex of T with minimum parsimony score.

Binary Characters

		Characters				
		1	2	3	4	5
Species	A	0	1	1	0	0
	B	0	0	1	1	0
	C	1	1	1	1	0
	D	1	1	0	1	1

Characters only have
two possible states

Possible Encoding:
0 : not-mutated
1 : mutated

Possible Encoding:
0 : no wings
1 : wings

Binary Characters

		Characters				
		1	2	3	4	5
Species	A	0	1	1	0	0
	B	0	0	1	1	0
	C	1	1	1	1	0
	D	1	1	0	1	1

Characters only have two possible states

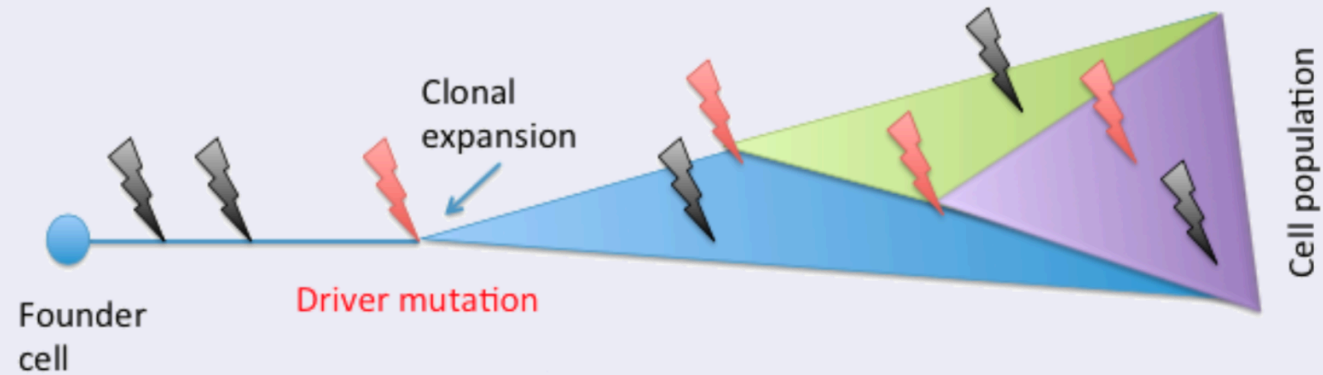
Possible Encoding:
0 : not-mutated
1 : mutated

Possible Encoding:
0 : no wings
1 : wings

Question: Given n binary characters, what is the smallest parsimony score?

Somatic Mutations and Cancer

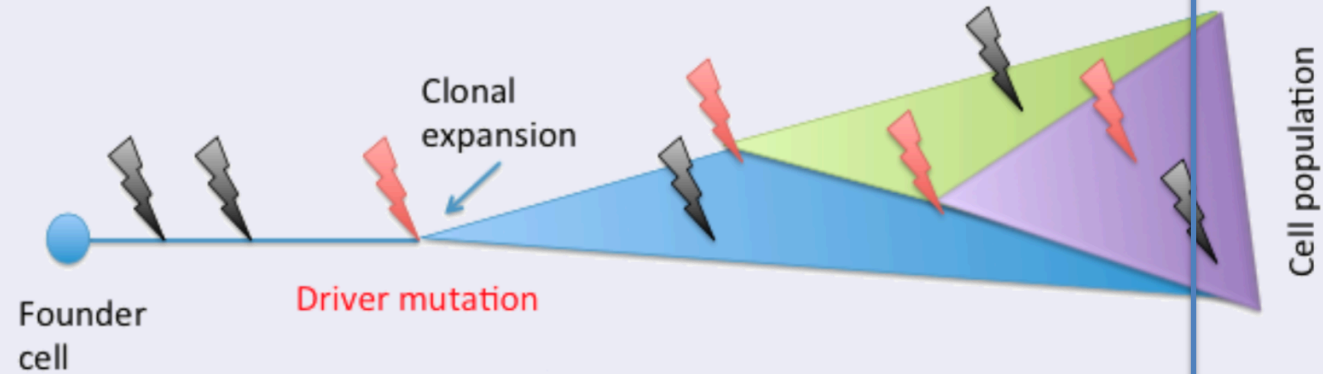
Clonal theory of cancer (Nowell, 1976)



“typical tumor”: ~10 driver mutations
 100’s – 1000’s of passenger mutations

Somatic Mutations and Cancer

Clonal theory of cancer (Nowell, 1976)



“typical tumor”: ~10 driver mutations
100’s – 1000’s of passenger mutations



International
Cancer Genome
Consortium



Sequence genome

Progression of Somatic Mutations

Single nucleotide mutation

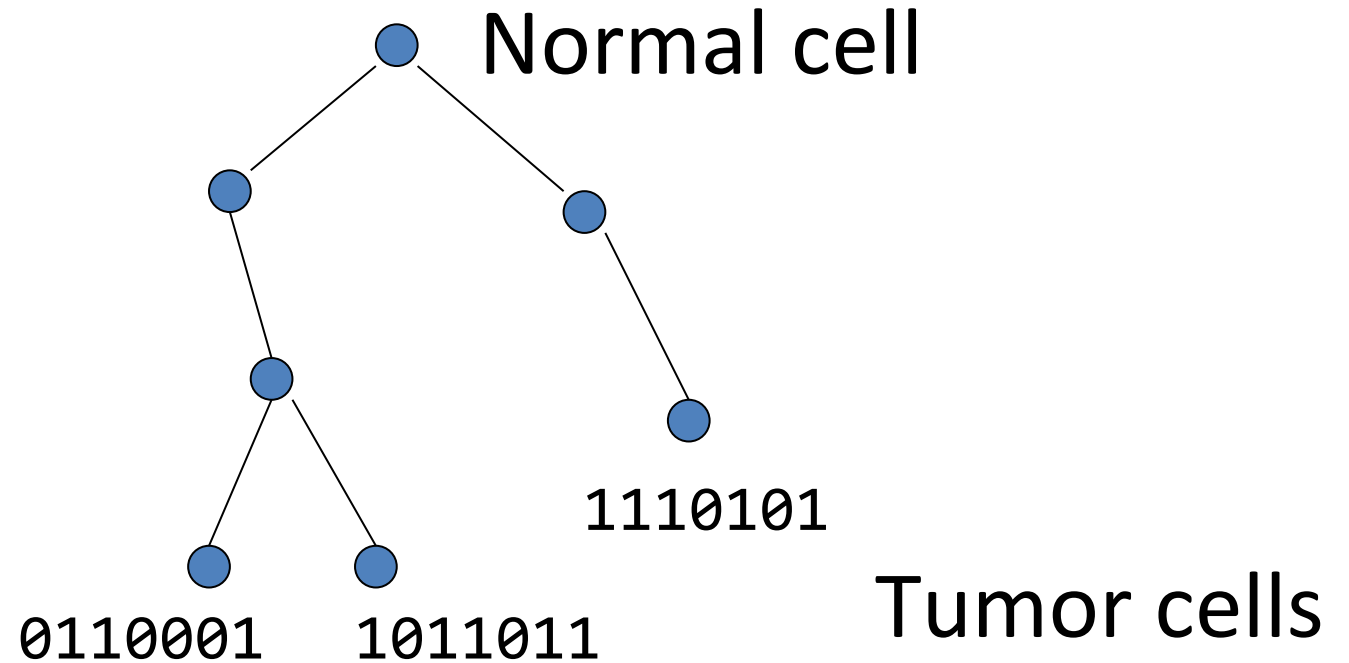
... CGT**A**TTAG ...



... CGT**C**TTAG ...

0 = normal

1 = mutated



Root is the normal, founder cell and leaves are cells in tumor.

Progression of Somatic Mutations

Single nucleotide mutation

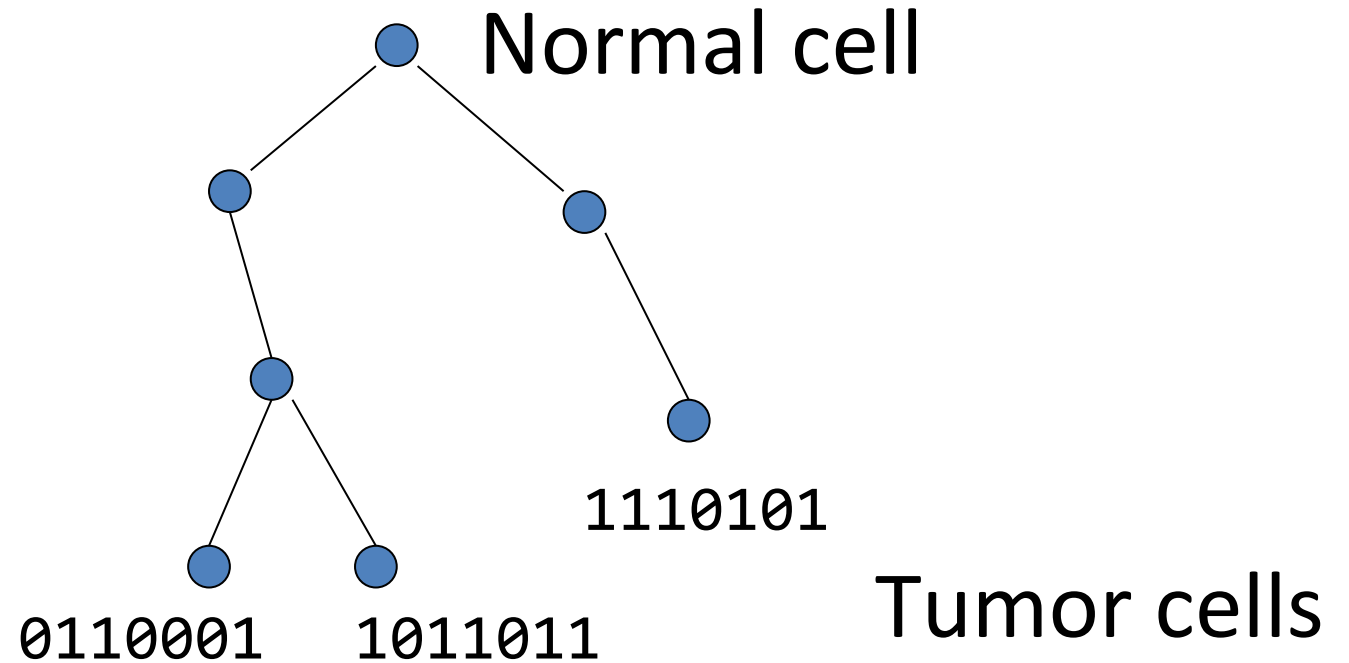
... CGT**A**TTAG ...



... CGT**C**ATTAG ...

0 = normal

1 = mutated

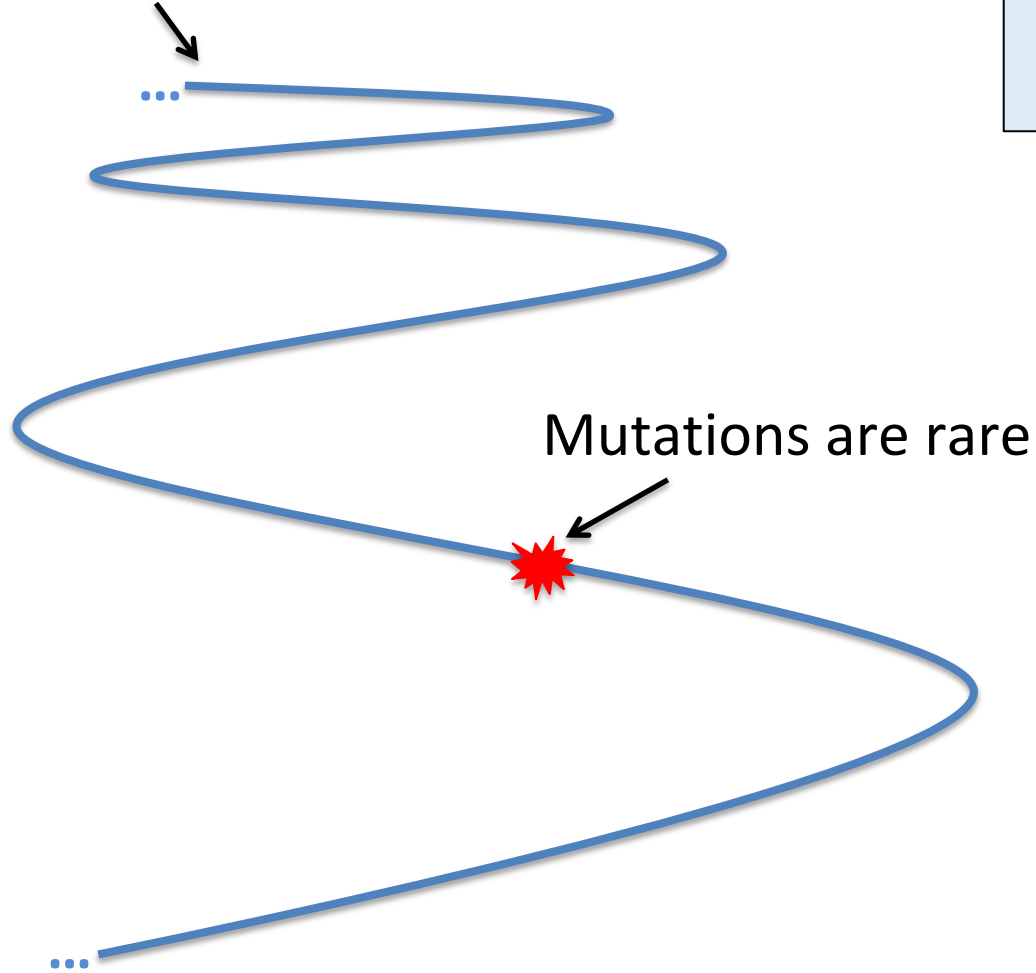


Root is the normal, founder cell and leaves are cells in tumor.

Infinite sites assumption: each locus mutates only once.







Infinite Sites Model = Two-state Perfect Phylogeny

The genome is large



[Kimura, 1969]

Infinite sites model: multiple mutations never occur at the same position

		Mutated Loci					
							
Species (cancer cells)	A	0	0	0	0	1	1
	B	0	0	0	1	1	1
	C	0	0	1	0	1	0
	D	1	0	0	0	0	0
	E	1	1	0	0	0	0

1: mutated

0: not

All sites are bi-allelic: mutated or not.

Two-state Perfect Phylogeny

Matrix $M \in \{0, 1\}^{n \times m}$ has n **taxa** and m **characters**

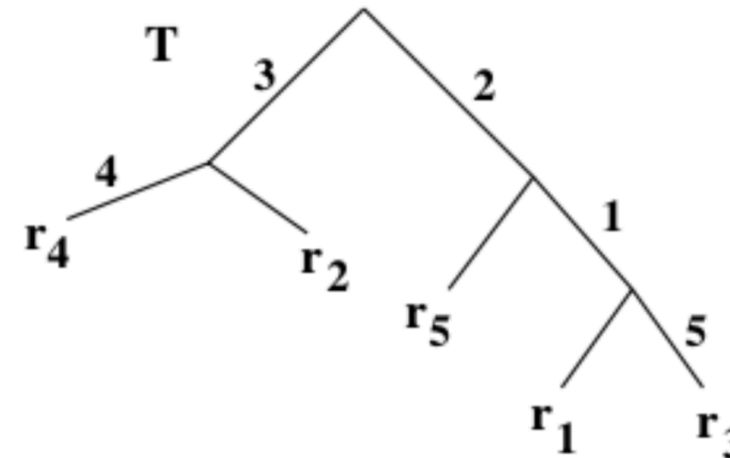
- Taxon f has state 1 for character c
 $\Leftrightarrow f$ **possesses** character c

	c_1	c_2	c_3	c_4	c_5
r_1	1	1	0	0	0
r_2	0	0	1	0	0
r_3	1	1	0	0	1
r_4	0	0	1	1	0
r_5	0	1	0	0	0

Definition

A **perfect phylogeny** for M is a rooted tree T with n leaves such that:

- 1 Each taxon labels only one leaf
- 2 Each character labels only one edge
- 3 Character possessed by a taxon are on unique path to root



Root node is all zero ancestor

Two-state Perfect Phylogeny Problem

Input:

Matrix $M \in \{0, 1\}^{n \times m}$ has n **taxa** and m **characters**

- Taxon f has state 1 for character c
 $\Leftrightarrow f$ **possesses** character c

	c_1	c_2	c_3	c_4	c_5
r_1	1	1	0	0	0
r_2	0	0	1	0	0
r_3	1	1	0	0	1
r_4	0	0	1	1	0
r_5	0	1	0	0	0

Problem

Given $M \in \{0, 1\}^{n \times m}$ does M have a perfect phylogeny?

Try it yourself!

Only one of these matrices can be used to build a perfect phylogeny.

- (1) As a group, **decide on an approach** to try to determine which one is which.
- (2) Try out your approach to see if you can construct the tree.
- (3) What did you learn from your attempt?

$M_1 =$

Species	Characters				
	C_1	C_2	C_3	C_4	C_5
A	0	1	0	0	0
B	0	0	1	0	0
C	1	1	0	0	0
D	0	0	1	1	0
E	1	1	0	0	1

$M_2 =$

Species	Characters				
	C_1	C_2	C_3	C_4	C_5
A	0	0	1	1	0
B	0	0	1	0	1
C	1	1	0	0	1
D	1	1	0	0	0
E	0	1	0	0	1

The Perfect Phylogeny Problem – Preliminaries

Problem

Given $M \in \{0, 1\}^{n \times m}$ does M have a perfect phylogeny?

Definition

$I(c)$ is the set of taxa that possess character c ; and $\sigma(f)$ is the set of characters possessed by taxon f .

	c_1	c_2	c_3	c_4	c_5		c_1 (2)	c_2 (1)	c_3 (3)	c_4 (5)	c_5 (4)
r_1	1	1	0	0	0	\Rightarrow	1	1	0	0	0
r_2	0	0	1	0	0		0	0	1	0	0
r_3	1	1	0	0	1		1	1	0	1	0
r_4	0	0	1	1	0		0	0	1	0	1
r_5	0	1	0	0	0		1	0	0	0	0

$$I(c_1) = \{r_1, r_3\}$$

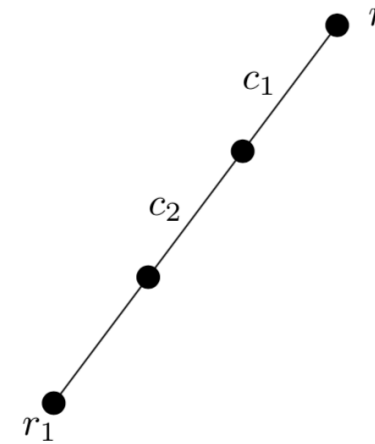
$$\sigma(r_1) = \{c_1, c_2\}$$

Sort columns of M s.t. $c < d$ iff $|I(c)| \geq |I(d)|$. Break ties arbitrarily.

- Consider rows of M iteratively
 - ▶ T_i is tree of first i rows of M
- T_1 is a path graph
 - ▶ Terminal nodes r and 1
 - ▶ $|\sigma(1)| + 1$ edges labeled by $\sigma(1)$

$$c < d \text{ iff } |I(c)| \geq |I(d)|$$

	c_1	c_2	c_3	c_4	c_5
r_1	1	1	0	0	0
r_2	0	0	1	0	0
r_3	1	1	0	1	0
r_4	0	0	1	0	1
r_5	1	0	0	0	0



- Consider rows of M iteratively

- T_i is tree of first i rows of M

- T_1 is a path graph

- Terminal nodes r and 1

- $|\sigma(1)| + 1$ edges labeled by $\sigma(1)$

- T_{i+1} is a supertree of T_i

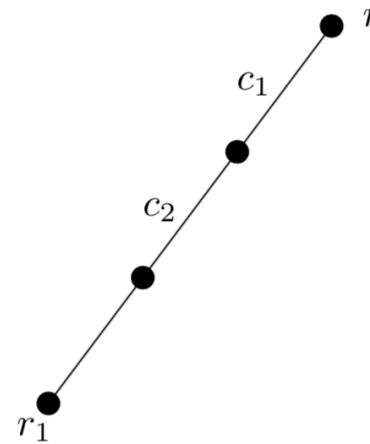
- Let v be last node on walk from r matching characters $\sigma(i+1)$

- ★ Character d is the last match

- ★ Unmatched characters $\tau(i+1)$

$$c < d \text{ iff } |I(c)| \geq |I(d)|$$

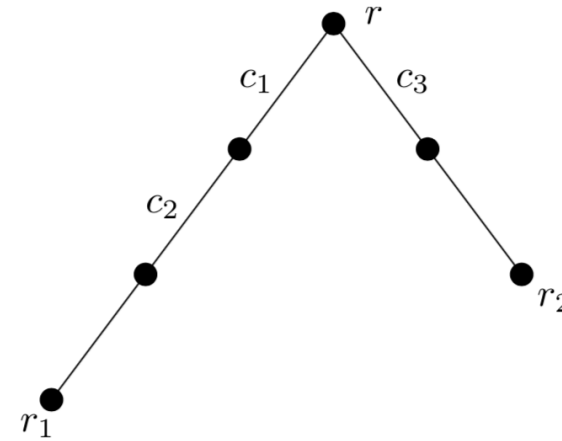
	c_1	c_2	c_3	c_4	c_5
r_1	1	1	0	0	0
r_2	0	0	1	0	0
r_3	1	1	0	1	0
r_4	0	0	1	0	1
r_5	1	0	0	0	0



- Consider rows of M iteratively
 - T_i is tree of first i rows of M
- T_1 is a path graph
 - Terminal nodes r and 1
 - $|\sigma(1)| + 1$ edges labeled by $\sigma(1)$
- T_{i+1} is a supertree of T_i
 - Let v be last node on walk from r matching characters $\sigma(i+1)$
 - ★ Character d is the last match
 - ★ Unmatched characters $\tau(i+1)$
 - Extend T_i with path Π
 - ★ Π has terminals v and $i+1$
 - ★ Π has $|\tau(i+1)| + 1$ edges labeled by $\tau(i+1)$

$$c < d \text{ iff } |I(c)| \geq |I(d)|$$

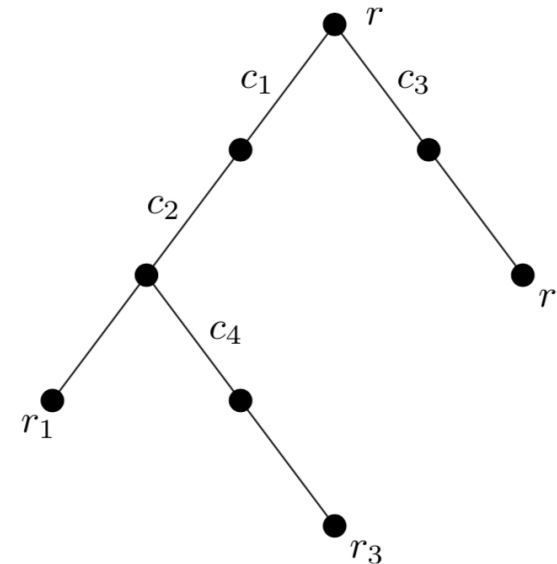
	c_1	c_2	c_3	c_4	c_5
r_1	1	1	0	0	0
r_2	0	0	1	0	0
r_3	1	1	0	1	0
r_4	0	0	1	0	1
r_5	1	0	0	0	0



- Consider rows of M iteratively
 - T_i is tree of first i rows of M
- T_1 is a path graph
 - Terminal nodes r and 1
 - $|\sigma(1)| + 1$ edges labeled by $\sigma(1)$
- T_{i+1} is a supertree of T_i
 - Let v be last node on walk from r matching characters $\sigma(i+1)$
 - ★ Character d is the last match
 - ★ Unmatched characters $\tau(i+1)$
 - Extend T_i with path Π
 - ★ Π has terminals v and $i+1$
 - ★ Π has $|\tau(i+1)| + 1$ edges labeled by $\tau(i+1)$

$$c < d \text{ iff } |I(c)| \geq |I(d)|$$

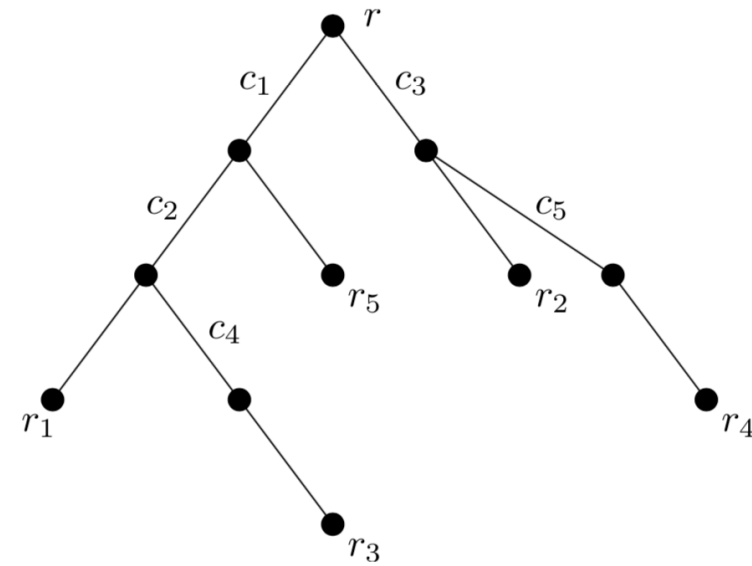
	c_1	c_2	c_3	c_4	c_5
r_1	1	1	0	0	0
r_2	0	0	1	0	0
r_3	1	1	0	1	0
r_4	0	0	1	0	1
r_5	1	0	0	0	0



- Consider rows of M iteratively
 - T_i is tree of first i rows of M
- T_1 is a path graph
 - Terminal nodes r and 1
 - $|\sigma(1)| + 1$ edges labeled by $\sigma(1)$
- T_{i+1} is a supertree of T_i
 - Let v be last node on walk from r matching characters $\sigma(i+1)$
 - ★ Character d is the last match
 - ★ Unmatched characters $\tau(i+1)$
 - Extend T_i with path Π
 - ★ Π has terminals v and $i+1$
 - ★ Π has $|\tau(i+1)| + 1$ edges labeled by $\tau(i+1)$

$$c < d \text{ iff } |I(c)| \geq |I(d)|$$

	c_1	c_2	c_3	c_4	c_5
r_1	1	1	0	0	0
r_2	0	0	1	0	0
r_3	1	1	0	1	0
r_4	0	0	1	0	1
r_5	1	0	0	0	0



Lemma

Let $M_i \in \{0, 1\}^{i \times m}$ be a submatrix of M . If M is conflict-free then T_i is a perfect phylogeny for M_i .

Outline

- Two-State Perfect Phylogeny
- Multi-State Perfect Phylogeny
- Large Maximum Parsimony Phylogeny Problem
- Summary

Reading:

- Lecture notes

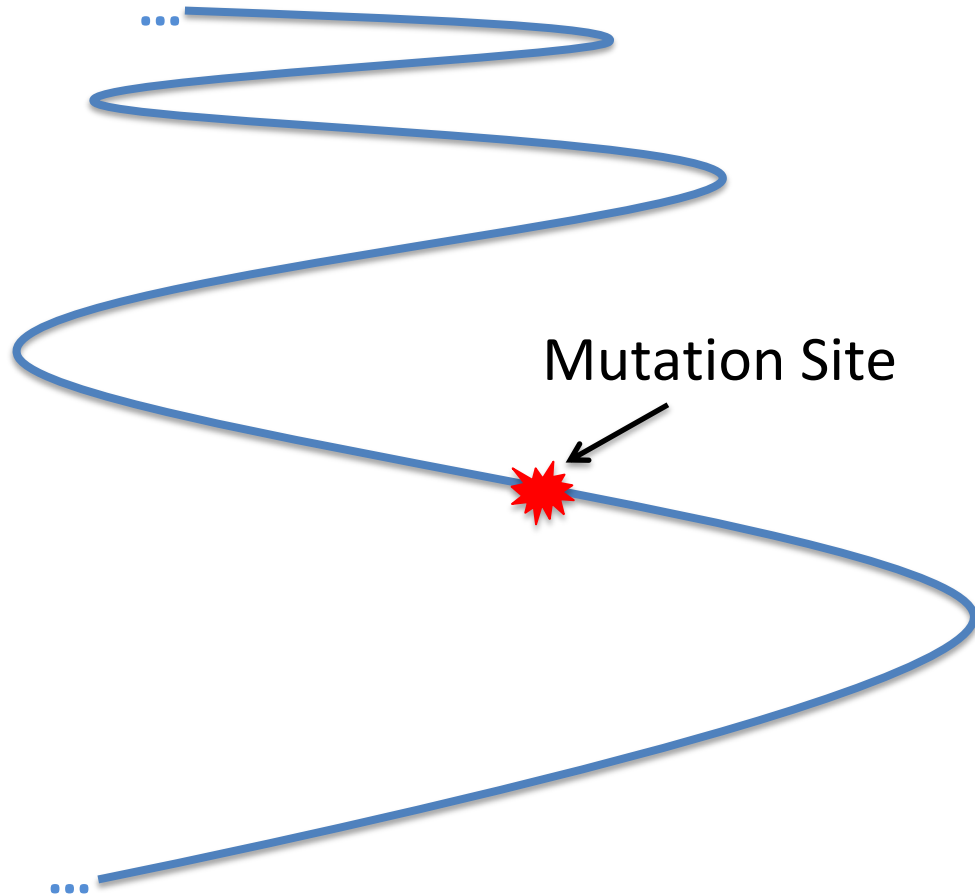
Integer Characters

		Characters				
		1	2	3	4	5
Species	A	2	1	1	0	0
	B	0	2	1	2	2
	C	1	2	1	1	1
	D	1	1	0	1	2

Characters have k
possible states

Question: Given n integer characters with k states,
what is the smallest parsimony score?

Infinite Alleles Model = Multi-state Perfect Phylogeny



Infinite alleles model:

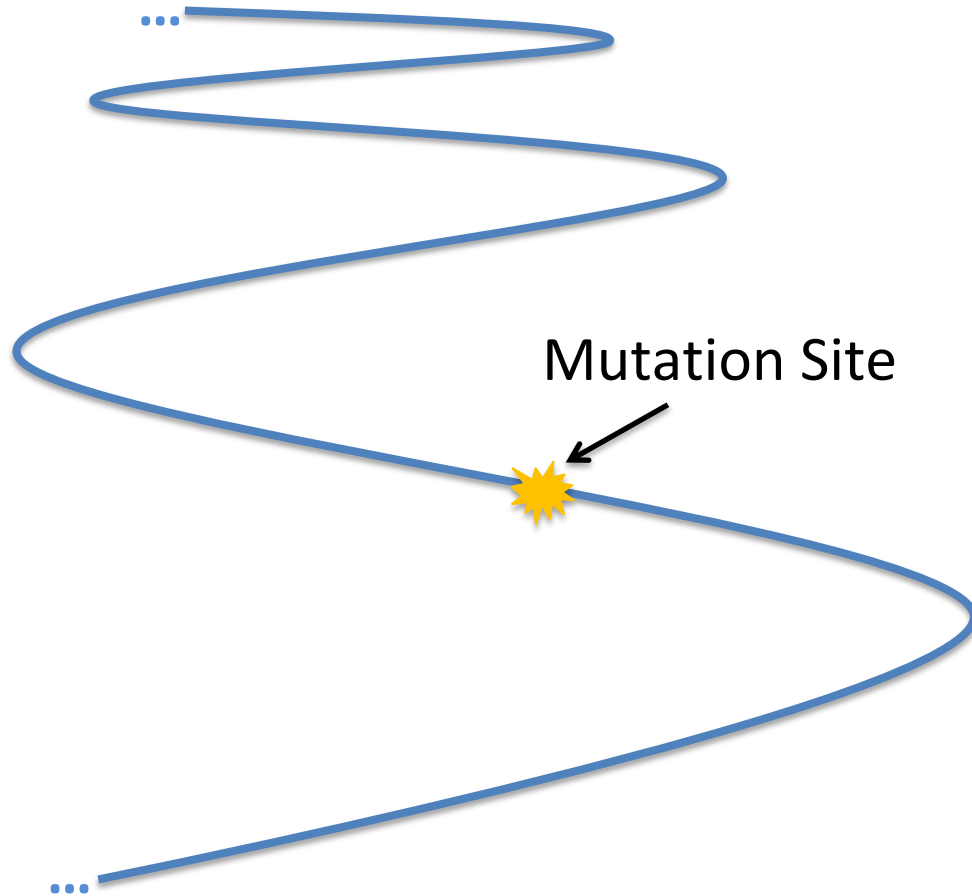
- For any mutation, there are an infinite number of possibilities of what mutation looks like (states).
- So, the same position can be mutated multiple times, but it never mutates to the same “allele” or state.

Site History:



Characters have integer states

Infinite Alleles Model = Multi-state Perfect Phylogeny



Infinite alleles model:

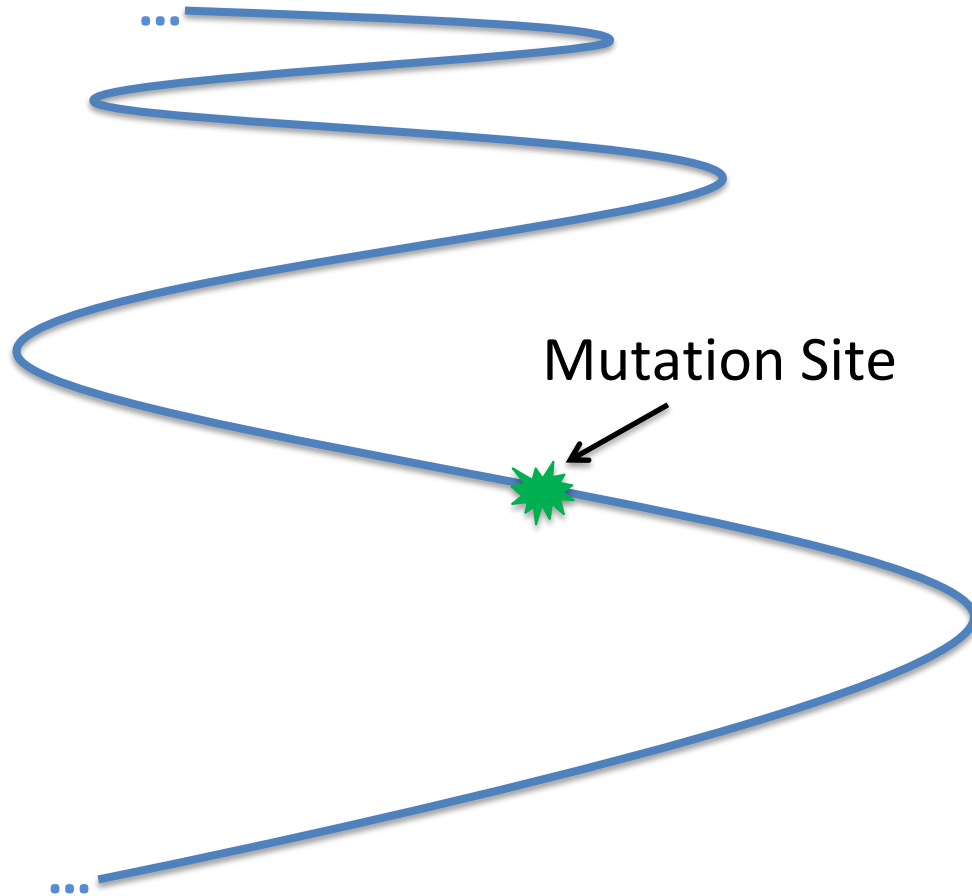
- For any mutation, there are an infinite number of possibilities of what mutation looks like (states).
- So, the same position can be mutated multiple times, but it never mutates to the same “allele” or state.

Site History:



Characters have integer states

Infinite Alleles Model = Multi-state Perfect Phylogeny



Infinite alleles model:

- For any mutation, there are an infinite number of possibilities of what mutation looks like (states).
- So, the same position can be mutated multiple times, but it never mutates to the same “allele” or state.

Site History:



Characters have integer states

Multi-state Perfect Phylogeny

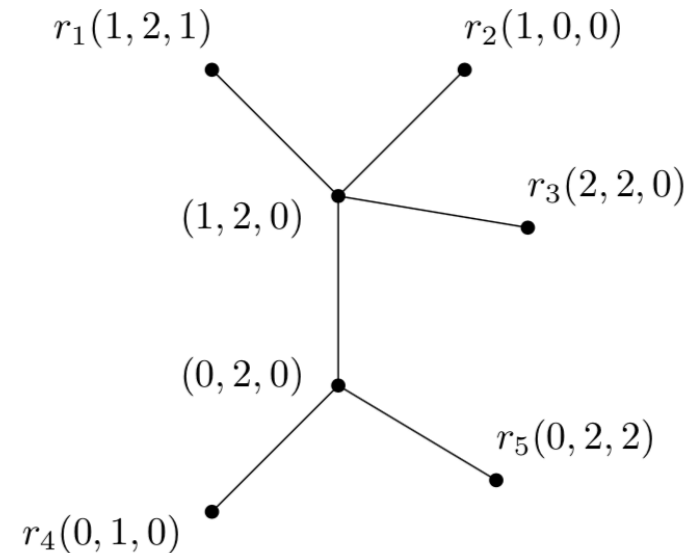
Matrix $M \in \{0, \dots, k-1\}^{n \times m}$ has
 n taxa and m characters

	c_1	c_2	c_3
r_1	1	2	1
r_2	1	0	0
r_3	2	2	0
r_4	0	1	0
r_5	0	2	2

Definition

A **multi-state perfect phylogeny** for M is a tree T with n leaves such that:

- 1 Each taxon labels exactly one leaf
- 2 Each node is labeled by $\{0, \dots, k-1\}^m$
- 3 Nodes labeled with state i for character c form a connected subtree $T_c(i)$



Theorem (Bodlaender et al., 1992) [Bodlaender, Fellows and Warnow]

For general k , the multi-state perfect phylogeny problem is NP-complete

Cladistic vs. Qualitative Characters

Definition

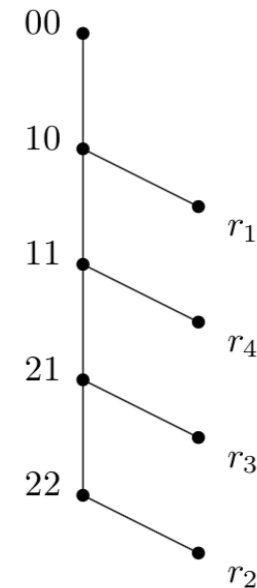
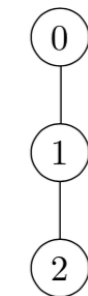
A **multi-state perfect phylogeny** for M is a tree T with n leaves such that:

- 1 Each taxon labels exactly one leaf
- 2 Each node is labeled by $\{0, \dots, k-1\}^m$
- 3 Nodes with state i for character c form a connected subtree $T_c(i)$

A **cladistic** character c has a **state tree** t_c on its states

A phylogeny T is **consistent** if the reduced tree $\sigma(T, c)$ is identical with t_c for all c

	a	b
r_1	1	0
r_2	2	2
r_3	2	1
r_4	1	1



Cladistic vs. Qualitative Characters

Definition

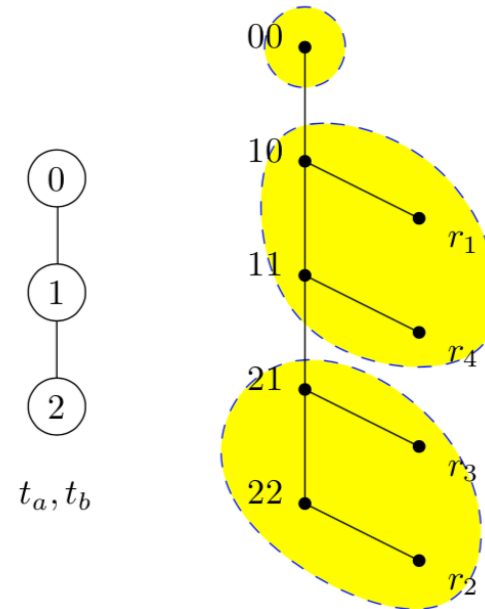
A **multi-state perfect phylogeny** for M is a tree T with n leaves such that:

- 1 Each taxon labels exactly one leaf
- 2 Each node is labeled by $\{0, \dots, k-1\}^m$
- 3 Nodes with state i for character c form a connected subtree $T_c(i)$

A **cladistic** character c has a **state tree** t_c on its states

A phylogeny T is **consistent** if the reduced tree $\sigma(T, c)$ is identical with t_c for all c

	a	b
r_1	1	0
r_2	2	2
r_3	2	1
r_4	1	1



Cladistic vs. Qualitative Characters

Definition

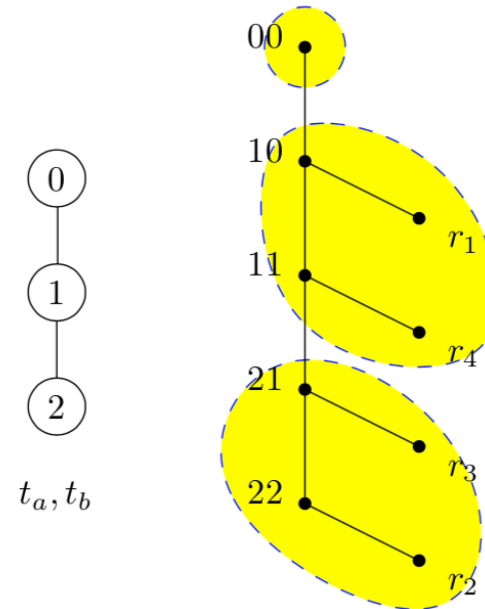
A **multi-state perfect phylogeny** for M is a tree T with n leaves such that:

- 1 Each taxon labels exactly one leaf
- 2 Each node is labeled by $\{0, \dots, k-1\}^m$
- 3 Nodes with state i for character c form a connected subtree $T_c(i)$

A **cladistic** character c has a **state tree** t_c on its states

A phylogeny T is **consistent** if the reduced tree $\sigma(T, c)$ is identical with t_c for all c

	a	b
r_1	1	0
r_2	2	2
r_3	2	1
r_4	1	1



Multi-state Cladistic Perfect Phylogeny

Outline

- Two-State Perfect Phylogeny
- Multi-State Perfect Phylogeny
- Large Maximum Parsimony Phylogeny Problem
- Summary

Reading:

- Lecture notes

Small and a Large Problem

Small Maximum Parsimony Phylogeny Problem:

Given $m \times n$ matrix $A = [a_{i,j}]$ and tree T with m leaves, find assignment of character states to each internal vertex of T with minimum parsimony score.

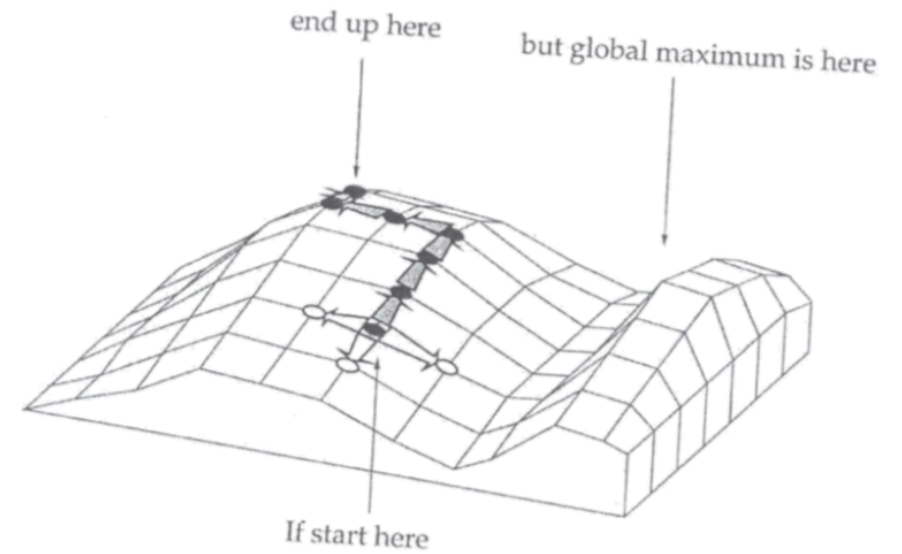
Large Maximum Parsimony Phylogeny Problem:

Given $m \times n$ matrix $A = [a_{i,j}]$, find a tree T with m leaves labeled according to A and an assignment of character states to each internal vertex of T with minimum parsimony score.

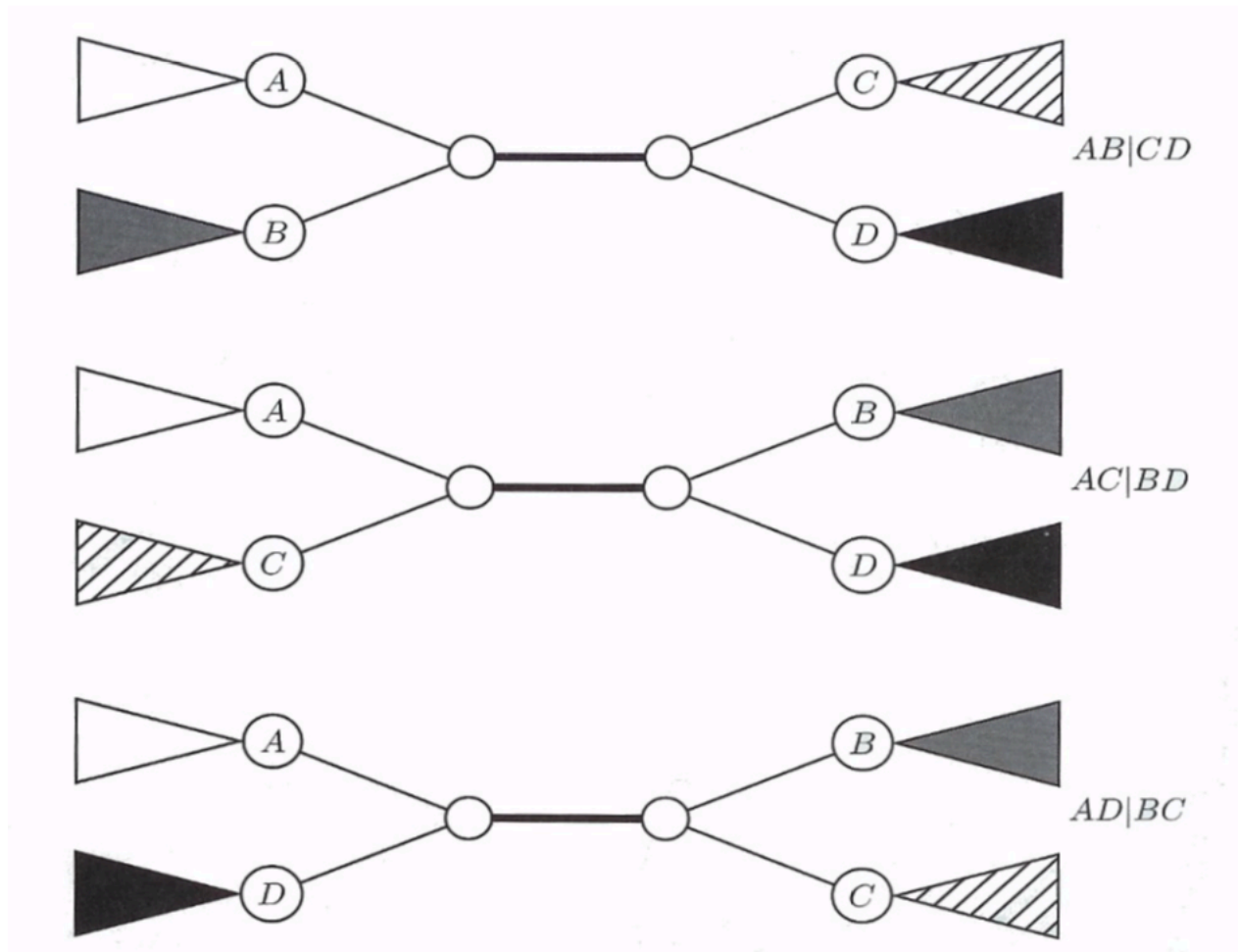
General Large Maximum Parsimony Phylogeny

- This problem is NP-hard
- Heuristics using local search (tree moves)
 1. Start with an arbitrary tree T .
 2. Check “neighbors” of T .
 3. Move to a neighbor if it provides the best improvement in parsimony/likelihood score.

Caveats:
Could be stuck in **local** optimum, and not achieve global optimum



Example: Nearest-Neighbor Interchange (NNI)



Rearrange four subtrees
defined by one
internal edge

Figure: Jones and Pevzner

Outline

- Two-State Perfect Phylogeny
- Multi-State Perfect Phylogeny
- Large Maximum Parsimony Phylogeny Problem
- Summary

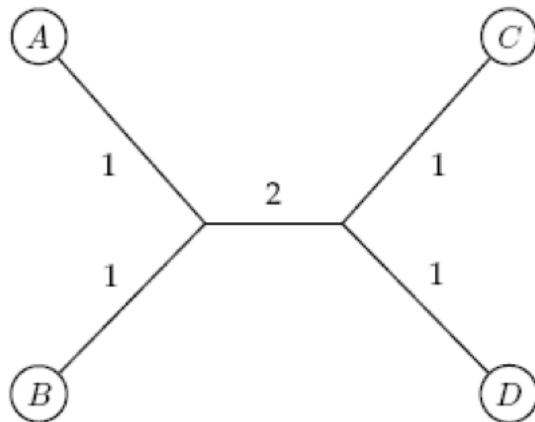
Reading:

- Lecture notes

Distance-based Phylogeny

- Small additive distance phylogeny problem
 - In P
 - Recursive algorithm using neighboring leaves
- Large additive distance phylogeny problem
 - In P -- two algorithms:
 1. Find degenerate triples and resolve these
 2. Neighbor joining: identifies neighboring leaves even when tree is not given
 - Complete characterization of additive matrices using the four-point condition

	A	B	C	D
A	0	2	4	4
B	2	0	4	4
C	4	4	0	2
D	4	4	2	0



Character-based Phylogeny

- Small maximum parsimony problem
 - Sankoff algorithm: dynamic programming
- Two-state perfect phylogeny problem
 - In P: $O(mn)$ time
 - Complete characterization as conflict free binary matrices
- Multi-state perfect phylogeny problem
 - NP-hard in general
 - In P given state trees
- Large maximum parsimony problem
 - NP-hard
 - Heuristic using local search